

## INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.

PCT/EP 99/07551

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9837874 A1	03/09/98	AU 2796797 A	19/11/97
		AU 6295198 A	18/09/98
		EP 0898823 A	03/03/99
		NO 994109 D	00/00/00
		SE 9700708 A	28/08/98
EP 0770385 A1	02/05/97	AU 7040496 A	01/05/97
		JP 9124470 A	13/05/97
		SG 43432 A	17/10/97
WO 9623489 A2	08/08/96	AU 4715796 A	21/08/96
		CA 2210957 A	08/08/96
		DE 19503604 A	08/08/96
		EP 0806946 A	19/11/97
		JP 10513444 T	22/12/98
		US 5886053 A	23/03/99
		DE 19539743 A	30/04/97
WO 9500130 A1	05/01/95	AU 7005694 A	17/01/95
		GB 2280110 A,B	25/01/95
		GB 9412938 D	00/00/00
		IL 110139 D	00/00/00
		ZA 9404633 A	25/10/95

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

NILSSON, Brita  
Stockholms Patentbyrå Zacco AB  
P.O. Box 23101  
S-104 35 Stockholm  
SUÈDE

Date of mailing (day/month/year) 29 June 2001 (29.06.01)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference 29805/BN	
International application No. PCT/EP99/07551	International filing date (day/month/year) 08 October 1999 (08.10.99)

## 1. The following indications appeared on record concerning:

☐ the applicant
                 
 ☐ the inventor
                 
 ☒ the agent
                 
 ☐ the common representative

## Name and Address

NILSSON, Brita  
AB Stockholms Patentbyrå, Zacco &  
Bruhn  
P.O. Box 23101  
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Sweden

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person
                 
 ☐ the name
                 
 ☒ the address
                 
 ☐ the nationality
                 
 ☐ the residence

## Name and Address

NILSSON, Brita  
Stockholms Patentbyrå Zacco AB  
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Sweden

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Anman QIU

Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

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## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 06 June 2000 (06.06.00)	
<b>International application No.</b> PCT/EP99/07551	<b>Applicant's or agent's file reference</b> 29805/BN
<b>International filing date</b> (day/month/year) 08 October 1999 (08.10.99)	<b>Priority date</b> (day/month/year) 16 October 1998 (16.10.98)
<b>Applicant</b> LIGNELL, Åke	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

10 May 2000 (10.05.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Juan Cruz

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International Bureau



5000

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification 7 :</b> A61K 31/122, 31/07, A61P 1/00, 39/06		<b>A1</b>	<b>(11) International Publication Number:</b> WO 00/23064
			<b>(43) International Publication Date:</b> 27 April 2000 (2004.00)
<b>(21) International Application Number:</b> PCT/EP99/07551 <b>(22) International Filing Date:</b> 8 October 1999 (08.10.99)  <b>(30) Priority Data:</b> 9803541-3      16 October 1998 (16.10.98)      SE  <b>(71) Applicant (for all designated States except US):</b> ASTAC-AROTENE AB [SE/SE]; Idrottsvägen 4, S-134 40 Gustavsberg (SE).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> LIGNELL, Åke [SE/SE]; Klippstigen 5, S-139 40 Värmdö (SE).  <b>(74) Agents:</b> NILSSON, Brita et al.; AB Stockholms Patentbyrå, Zacco & Bruhn, P.O. Box 23101, S-104 35 Stockholm (SE).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PA, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
<b>(54) Title:</b> TREATMENT OF DYSPEPSIA			
<b>(57) Abstract</b>  Use of a at least one type of xanthophylls for the preparation of a medicament for prophylactic and/or therapeutic treatment of dyspepsia, is disclosed. The xanthophyll is preferably astaxanthin, e.g. astaxanthin is in a form esterified with fatty acids, such as in algal meal prepared from a culture of the alga <i>Haematococcus sp.</i> The medicament may further comprise carbohydrate structures and/or (a) different antioxidant(s). Further, a method of prophylactic and/or therapeutic treatment of dyspepsia in an individual, is described. The method comprises administration to said individual of a dyspepsia-alleviating amount of a medicament comprising at least one type of xanthophylls.			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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## **TREATMENT OF DYSPEPSIA**

5           The present invention relates to treatment of dyspepsia. The invention is particularly concerned with the use of at least one type of xanthophylls for the preparation of a medicament for prophylactic and/or therapeutic treatment of dyspepsia, and a method of treating dyspepsia. A preferred xanthophyll is astaxanthin.

### **10   Background of the invention**

Dyspepsia, or indigestion, is one of the most common gastrointestinal disorders or diseases in both animals and humans. Dyspepsia is persistent or recurrent abdominal pain or abdominal discomfort centered in the upper abdomen. Dyspepsia refers to symptoms in the upper abdomen that are considered to be related to the upper alimentary tract. Often dyspepsia  
15 is temporary and disappears spontaneously. In case alleviation of the symptoms is desired, ingestion of antacids is often the first choice of treatment. Antacids are normally not taken prophylactically.

However, there are several alternative therapeutic treatments of dyspepsia, and the present invention provides a new alternative, which may also be used for prophylactic  
20 treatment.

### **Description of the invention**

The present invention is directed to the use of at least one type of xanthophylls for the preparation of a medicament for prophylactic and/or therapeutic treatment of  
25 dyspepsia.

In a preferred embodiment the xanthophyll is astaxanthin, especially astaxanthin in a form esterified with fatty acids. The astaxanthin in esterified form is suitably provided in the form of algal meal prepared from a culture of the alga *Haematococcus sp.*

The medicament may further comprise carbohydrate structures, such as  
30 lipopolysaccharides, polysaccharides and glycoproteins, and/ or one or several different antioxidant(s), such as ascorbic acid (vitamin C) and tocopherol (vitamin E).

The medicament is preferably in the form of unit doses adapted for a daily dosage of xanthophyll(s) in the range of 0.05 to 1 mg per kg body weight of an individual, which is an animal or a human.

The invention is also directed to a method of prophylactic and/or therapeutic treatment of dyspepsia in an individual, which comprises administration to said individual of an dyspepsia-alleviating amount of a medicament comprising at least one type of xanthophylls.

5 In a preferred embodiment the xanthophyll is astaxanthin, especially astaxanthin in a form esterified with fatty acids. The astaxanthin in esterified form is suitably provided in the form of algal meal prepared from a culture of the alga *Haematococcus sp.*

The medicament may further comprise carbohydrate structures, such as lipopolysaccharides, polysaccharides and glycoproteins, and/ or one or several different  
10 antioxidant(s), such as ascorbic acid (vitamin C) and tocopherol (vitamin E).

Preferably, the dyspepsia-alleviating amount of the medicament comprises xanthophyll(s) in the range of 0.05 to 1 mg per kg body weight of the individual, which is an animal or a human.

The at least one type of xanthophylls that are used in the present invention may  
15 comprise a mixture of different types of xanthophylls or different forms of the same xanthophyll, such as a mixture of synthetic astaxanthin and naturally produced astaxanthin.

The mechanism of the prophylactic and therapeutic effect of the xanthophylls in the treatment of dyspepsia is not known, but it should be noted that they possess strong antioxidative properties and that they are soluble in fats and oils.

20 At present, the most preferred embodiment of the invention comprises algal meal having astaxanthin in esterified form with fatty acids dissolved in small droplets of naturally occurring oil and naturally occurring carbohydrate structures in the partially disrupted cell walls.

The medicament used in the invention may comprise additional ingredients  
25 which are pharmacologically acceptable inactive or active in prophylactic and/or therapeutic use, such as flavoring agents.

The medicament may be presented in a separate unit dose or in mixture with food. Examples of separate unit doses are tablets, gelatin capsules and predetermined amounts of solutions, e. g. oil solutions, or emulsions, e.g. water-in- oil or oil-in-water emulsions.  
30 Examples of foods in which the preparation of the invention may be incorporated is dairy products, such as yoghurt, chocolate and cereals.

## Experiments

The experiments were conducted on 15 human volunteers experiencing symptoms of dyspepsia that did not disappear spontaneously. They were given 2 to 10 capsules per day containing algal meal produced by culturing of the algae *Haematococcus sp.* by AstaCarotene AB, Gustavsberg, Sweden. (These capsules are sold as an anti-oxidant and they contain 4 mg astaxanthin per capsule, with the instruction to take one capsule per day.)

This double to ten times the recommended dose, i.e. 8 - 40 mg astaxanthin per day, eliminated or drastically alleviated the symptoms of dyspepsia in all volunteers in 1 - 3 weeks, and no side effects were reported.

Astaxanthin from other sources, and other xanthophylls as well, are expected to be similarly useful for the purposes of the invention. An advantage of using astaxanthin from algae is, however, that the astaxanthin exists in a form esterified with fatty acids [Renström B. et al, 1981, Phytochem 20(11) :2561-2564], which esterified astaxanthin thereby is more stable during handling and storage than free astaxanthin.

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## CLAIMS

1. Use of a at least one type of xanthophylls for the preparation of a medicament for prophylactic and/or therapeutic treatment of dyspepsia.

5        2. Use according to claim 1, wherein the xanthophyll is astaxanthin.

3. Use according to claim 2, wherein the astaxanthin is in a form esterified with fatty acids.

4. Use according to claim 3, wherein the astaxanthin in esterified form is provided in the form of algal meal prepared from a culture of the alga *Haematococcus sp.*

10       5. Use according to any one of claims 1 - 4, wherein the medicament further comprises carbohydrate structures.

6. Use according to any one of claims 1 - 5, wherein the medicament further comprises (a) different antioxidant(s).

15       7. Use according to any one of claims 1 - 6, wherein the medicament is in the form of unit doses adapted for a daily dosage of xanthophyll(s) in the range of 0.05 to 1 mg per kg body weight of an individual.

8. Method of prophylactic and/or therapeutic treatment of dyspepsia in an individual, which comprises administration to said individual of an dyspepsia-alleviating amount of a medicament comprising at least one type of xanthophylls.

20       9. Method according to claim 8, wherein the xanthophyll is astaxanthin.

10. Method according to claim 9, wherein the astaxanthin is in a form esterified with fatty acids.

11. Method according to claim 10, wherein the astaxanthin in esterified form is provided in the form of algal meal prepared from a culture of the alga *Haematococcus sp.*

25       12. Method according claim 8, wherein the medicament further comprises carbohydrate structures.

13. Method according to claim 8, wherein the medicament further comprises (a) different antioxidant(s).

30       14. Method according to claim 8, wherein the dyspepsia-alleviating amount of the medicament comprises xanthophyll(s) in the range of 0.05 to 1 mg per kg body weight of the individual.

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# INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/EP 99/07551

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/122 A61K31/07 A61P1/00 A61P39/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 37874 A (ALEJUNG PAER ;ASTACAROTENE AB (SE); WADSTROEM TORKEK (SE)) 3 September 1998 (1998-09-03) the whole document	1-14
X	EP 0 770 385 A (SUNTORY LTD ;ITANO REFRIGERATED FOOD CO LTD (JP)) 2 May 1997 (1997-05-02) page 5, line 12 - line 55 page 6, line 48 -page 7, line 7; claims	1-14



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

27 January 2000

Date of mailing of the international search report

10. 03. 2000

Name and mailing address of the ISA

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Authorized officer

Gerd Strandell / MR

## INTERNATIONAL SEARCH REPORT

Internat. Application No.

PCT/EP 99/07551

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE STN MOZSIK G ET AL: "Retinoids as scavengers and gastric cytoprotection in animals, human beings and patients with peptic ulcer" retrieved from BIOSIS, accession no. 1993:537623 Database accession no. 199345124717 XP002900836 abstract page 329 -page 338 & OXYGEN FREE RADICALS AND SCAVENGERS IN THE NEUTRAL SCIENCES,1993, pages 329-338, ---	1-14
X	WO 96 23489 A (BASF AG ;SCHMUTZLER WOLFGANG (DE); KOLTER KARL (DE)) 8 August 1996 (1996-08-08) page 1 page 3, line 14 - line 38; claim 1 ---	1-14
A	WO 95 00130 A (HOWARD FOUNDATION ;HOWARD ALAN NORMAN (GB); HEPWORTH LAWRENCE BRYE) 5 January 1995 (1995-01-05) page 7, line 15 page 8, line 1 - line 17 page 9, line 11 - line 17; claims 1-4,10,13-18,23 -----	1-14

# INTERNATIONAL SEARCH REPORT

In ternational application No.

PCT/EP 99/ 07551

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 8-14 relate to methods of treatment of the human/animal body by surgery or by therapy (PCT Rule 39.1(iv)), the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.

PCT/EP 99/07551

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9837874	A1	03/09/98	AU	2796797 A	19/11/97
				AU	6295198 A	18/09/98
				EP	0898823 A	03/03/99
				NO	994109 D	00/00/00
				SE	9700708 A	28/08/98
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EP	0770385	A1	02/05/97	AU	7040496 A	01/05/97
				JP	9124470 A	13/05/97
				SG	43432 A	17/10/97
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WO	9623489	A2	08/08/96	AU	4715796 A	21/08/96
				CA	2210957 A	08/08/96
				DE	19503604 A	08/08/96
				EP	0806946 A	19/11/97
				JP	10513444 T	22/12/98
				US	5886053 A	23/03/99
				DE	19539743 A	30/04/97
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WO	9500130	A1	05/01/95	AU	7005694 A	17/01/95
				GB	2280110 A,B	25/01/95
				GB	9412938 D	00/00/00
				IL	110139 D	00/00/00
				ZA	9404633 A	25/10/95

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 29805/BN	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/07551	International filing date (day/month/year) 08/10/1999	Priority date (day/month/year) 16/10/1998
International Patent Classification (IPC) or national classification and IPC A61K31/122		
Applicant ASTACAROTENE AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  10/05/2000	Date of completion of this report  22.01.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Markopoulos, E  Telephone No. +49 89 2399 8658



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07551

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

### Description, pages:

1-3 as originally filed

### Claims, No.:

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07551

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 8-14 in regard to industrial applicability.

because:

- ☒ the said international application, or the said claims Nos. 8-14 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-14
	No: Claims -
Inventive step (IS)	Yes: Claims -
	No: Claims 1-14
Industrial applicability (IA)	Yes: Claims 1-7



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/07551

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No:      Claims    -

2. Citations and explanations  
**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 8-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:

D1: WO 98 37874 A (ALEJUNG PAER ;ASTACAROTENE AB (SE); WADSTROEM TORHEL (SE)) 3 September 1998 (1998-09-03)

D2: EP-A-0 770 385 (SUNTORY LTD ;ITANO REFRIGERATED FOOD CO LTD (JP)) 2 May 1997 (1997-05-02)

D3: WO 96 23489 A (BASF AG ;SCHMUTZLER WOLFGANG (DE); KOLTER KARL (DE)) 8 August 1996 (1996-08-08)

D4: DATABASE STN MOZSIK G ET AL: 'Retinoids as scavengers and gastric cytoprotection in animals, human beings and patients with peptic ulcer' retrieved from BIOSIS, accession no. 1993:537623 Database accession no. 199345124717 XP002900836 & OXYGEN FREE RADICALS AND SCAVENGERS IN THE NEUTRAL SCIENCES, 1993, pages 329-338,

2. D1 claims an oral preparation comprising at least one type of xanthophylls, preferably astaxanthin, for the treatment of inflammation in the mucous membrane of mammalian gastrointestinal (GI) tract caused by a Helicobacter sp. infection. This preparation is exactly the same as in the present application, e.g. astaxanthin is in a form esterified with fatty acids and deriving from a culture of the alga Haematococcus sp. and the preparation comprises further carbohydrate structures and antioxidants such as ascorbic acid (claims). The daily dosage is in the range of 0.01 to 10 mg per kg body weight (p. 4, l. 13-16).

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP99/07551

D2 describes the use of astaxanthin for the treatment of stress which can e.g. cause gastric and duodenal ulcers brought about by destruction of mucous membrane in the stomach and duodenum (p. 5, l. 50-52). Astaxanthin is being obtained e.g. by *Haematococcus* sp. (p. 4, l. 18-44), can be in esterified form (p. 5, l. 12-24), and is combined with an antioxidant (p. 7, l. 5-7).

D3 claims carotinoids like astaxanthin (p. 3, l. 25) for treating inflammatory diseases that are not caused by exposure to light or by microorganisms such as inflammation of the GI tract (p. 1, l. 24-26).

D4 discloses retinoids like lutein as scavengers and gastric cytoprotection in patients with peptic ulcers but different effects are being achieved in gastric and duodenal ulcers.

*H. pylori* is known to lead to dyspepsia, but not every infection with *H. pylori* shows symptoms. Likewise, inflammation in the GI tract can be a cause which can lead to dyspepsia, but this is not imperative. Therefore, claims 1-14 seem to be novel (Art. 33(2) PCT).

3. Since the major causes of dyspepsia are esophagitis, gastroesophageal reflux disease, peptic ulcer and functional dyspepsia which is defined as "chronic or recurrent upper gastrointestinal symptoms not explained by biochemical or structural abnormalities", i.e. that inflammation plays a role in the pathogenesis of dyspepsia, and it is known from D1-D3 to treat inflammation in the GI tract with xanthophylls such as astaxanthin, claims 1-14 cannot be considered as inventive (Art. 33(3) PCT).

Having defined the technical problem to be the finding of an alternative to the treatment of dyspepsia, the person skilled in the art will not be capable of acknowledging an inventive step vis-à-vis the disclosure of D1-D3: as soon as the diagnosis regarding the cause of the symptoms in a patient will be completed and in part of the cases inflammation will be responsible for dyspepsia, it is obvious to use a xanthophyll for the treatment, i.e. that in inflammation the skilled in the art would inevitably be prompted to use a xanthophyll.

Regarding the document cited by the applicant (Talley et al., GUT 1999;45(Suppl. 2):II37-II42) it has to be noted: first of all this document being a document published prior to the international filing date but later than the priority date claimed, cannot be considered for the time being, but taken the information known from the literature cited therein and since

the authors endorsed the original Rome definition of dyspepsia from 1991, the following can be said concerning dyspepsia in general:

Dyspepsia is subdivided into 3 subgroups whereby the first subgroup relates to identified causes for the symptoms e.g. esophagitis. Since the present application covers treatment of all three groups, esophagitis being an inflammation of the esophagus is included. Therefore and taking D1-D3 for treating inflammation, broad independent claims 1 and 8 cannot be seen as inventive.

Furthermore, claims 1-14 dealing with the treatment of any type of dyspepsia are not supported by special embodiments showing the effect of xanthophylls in e.g. dyspepsia caused by non GI causes such as cardiac disease. Actually, a conclusion is only made from one experiment with 15 test persons experiencing symptoms of dyspepsia whereby the cause is not known. The skilled person would act in the same way by deriving the teaching of D1-D4 without the exercise of inventive skill, in order to solve the problem posed.

In regard to non GI causes and especially to heart diseases, a relation between dyspepsia and cardiac disorders has been shown in e.g. Pasini et al., G. Clin. Med. 1989; 70(2):101-4. Even if one considers cardiac disease not being correlated to dyspepsia, it does not make a difference as to the lack of evidence that xanthophylls are useful in dyspepsia not being correlated to inflammation. An expansion on all groups of dyspepsia should have been supported by at least another experiment with a different group of patients.

Finally, the different inflammation pathways involved in the genesis of the disease or in producing symptoms resp. mentioned by the applicant, are not relevant for assessing inventive step, i.e. a different mechanism of action is not important since the final effect remains the same.

4. For the assessment of the present claims 8-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

## INTERNATIONAL-TYPE SEARCH REPORT

Search request No.

SE 98/01158

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/12, A61K 31/07

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI, BIOSIS, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9837874 A1 (ASTAC-AROTENE AB), 3 September 1998 (03.09.98) --	1-14
X	EP 0770385 A1 (SUNTORY LIMITED), 2 May 1997 (02.05.97), page 5, line 12 - line 55; page 6, line 48 - page 7, line 7, the claims --	1-14
X	STN International, File BIOSIS, BIOSIS accession no, 1993:537623, Document no. 199345124717, Mozsik, G. et al: "Retinoids as scavengers and gastric cytoprotection in animals, human beings and patients with peptic ulcer", Oxygen free radicals and scavengers in the natural sciences, 1993, pp 329-338 --	1-14

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international-type search

23 April 1999

Date of mailing of the international-type search report

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INTERNATIONAL-TYPE SEARCH REPORT

Search request No.

SE 98/01158

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9623489 A2 (BASF AKTIENGESELLSCHAFT), 8 August 1996 (08.08.96), page 1; page 3, line 14 - line 38, claim 1  --	1-14
A	WO 9500130 A1 (THE HOWARD FOUNDATION), 5 January 1995 (05.01.95), page 7, line 15; page 8, line 1 - line 17; page 9, line 11 - line 17, claims 1-4,10,13-18,23  --  -----	1-14

## INTERNATIONAL-TYPE SEARCH REPORT

Information on patent family members

02/03/99

Search request No.

SE 98/01158

WO	9837874	A1	03/09/98	AU	2796797 A	19/11/97
				AU	6295198 A	18/09/98
				SE	9700708 A	28/08/98
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EP	0770385	A1	02/05/97	AU	7040496 A	01/05/97
				JP	9124470 A	13/05/97
				SG	43432 A	17/10/97
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WO	9623489	A2	08/08/96	AU	4715796 A	21/08/96
				CA	2210957 A	08/08/96
				DE	19503604 A	08/08/96
				EP	0806946 A	19/11/97
				JP	10513444 T	22/12/98
				DE	19539743 A	30/04/97
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WO	9500130	A1	05/01/95	AU	7005694 A	17/01/95
				GB	2280110 A,B	25/01/95
				GB	9412938 D	00/00/00
				IL	110139 D	00/00/00
				ZA	9404633 A	25/10/95

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## PCT

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## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

09/463958

Applicant's or agent's file reference <b>29805/BN</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 99/ 07551</b>	International filing date (day/month/year) <b>08/10/1999</b>	(Earliest) Priority Date (day/month/year) <b>16/10/1998</b>
Applicant <b>ASTACAROTENE AB et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

## 4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

## 5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

## 6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.

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None of the figures.



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 07551

## B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark: Although claims 8-14 relate to methods of treatment of the human/animal body by surgery or by therapy (PCT Rule 39.1(iv)), the search has been carried out and based on the alleged effects of the compound/composition.**
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/07551

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/122 A61K31/07 A61P1/00 A61P39/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 37874 A (ALEJUNG PAER ;ASTACAROTENE AB (SE); WADSTROEM TORDEL (SE)) 3 September 1998 (1998-09-03) the whole document	1-14
X	EP 0 770 385 A (SUNTORY LTD ;ITANO REFRIGERATED FOOD CO LTD (JP)) 2 May 1997 (1997-05-02) page 5, line 12 - line 55 page 6, line 48 -page 7, line 7; claims -/--	1-14

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

27 January 2000

Date of mailing of the international search report

10. 03. 2000

Name and mailing address of the ISA

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Authorized officer

Gerd Strandell / MR

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE STN MOZSIK G ET AL: "Retinoids as scavengers and gastric cytoprotection in animals, human beings and patients with peptic ulcer" retrieved from BIOSIS, accession no. 1993:537623 Database accession no. 199345124717 XP002900836 abstract page 329 -page 338 &amp; OXYGEN FREE RADICALS AND SCAVENGERS IN THE NEUTRAL SCIENCES,1993, pages 329-338, ---</p>	1-14
X	<p>WO 96 23489 A (BASF AG ;SCHMUTZLER WOLFGANG (DE); KOLTER KARL (DE)) 8 August 1996 (1996-08-08) page 1 page 3, line 14 - line 38; claim 1 ---</p>	1-14
A	<p>WO 95 00130 A (HOWARD FOUNDATION ;HOWARD ALAN NORMAN (GB); HEPWORTH LAWRENCE BRYE) 5 January 1995 (1995-01-05) page 7, line 15 page 8, line 1 - line 17 page 9, line 11 - line 17; claims 1-4,10,13-18,23 -----</p>	1-14